# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 10 OCT 2005
WIPO

| Applicant's or agent's file reference | FOR FURTHER ACTION See Form PCT/IPEA/416 | |
|---|---|---|
| P13756 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/SE2004/001062 | 01.07.2004 | 01.07.2003 |
| International Patent Classification (IPC) or national classification and IPC | | |
| A61K 31/198 // A23L 1/305 | | |
| Applicant | | |
| Essentys AB et al | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02.05.2005 | 29.09.2005 |
| Name and mailing address of the IPEA/SE<br>Patent- och registreringsverket<br>Box 5055<br>S-102 42 STOCKHOLM<br>Facsimile No. +46 8 667 72 88 | Authorized officer<br>Ida Christensen/EÖ<br>Telephone No. +46 8 782 25 00 |

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/SE2004/001062

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-30 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* 1-3 received by this Authority on 31.08.2005
pages* _____ received by this Authority on _____

☒ the drawings:

pages 1/1 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing *(specify)*: _____
- ☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/SE2004/001062

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-12 (entirely)

because:

☒ the said international application, or the said claims Nos. 1-12 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001062

**Box No. V** **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 13-20 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 13-20 | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 13-20 | YES |
| | Claims | | NO |

2. Citations and explanations (Rule 70.7)

This report is based on the set of amended claims filed on 01-09-2005.

The aim of the present application is to use alpha-ketoglutaric acid (AKG) or derivatives thereof in order to A) decrease the absorption of glucose in plasma and thereby treat a high plasma glucose condition such as diabetes mellitus, and/or to
B) increase the absorption of amino acids and thereby treat a condition of malnutrition.

Reference will be made to the following documents cited in the International Search Report:

D1) Nephron 1996, 74: 261-265, Riedel E. et al
D2) EP 0922459
D3) Shambdu D. Varma et al, Molecular and Cellular Biochemistry 1997, 171: 23-28.

The aim of the study in D1 is to correct hyperphosphatemia and at the same time see if such treatment could improve amino acid metabolism and malnutrition as well. A combination of calcium carbonate and alpha-ketoglutarate is previously known as a potent phosphate-binding agent. D1 discloses that the administration of AKG with calcium carbonate effectively improves amino acid metabolism and furthers weight gain in hemodialysis patients, who have chronic renal failure and who frequently suffer from malnutrition (see the entire document).

.../...

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**
Continuation of: Box V

D2 relates to pharmaceutical compositions containing D-galactose and preferably alpha-ketoglutaric acid or a salt thereof, useful for treatment of metabolic stress conditions e.g. liver disorders, encephalopathies, eating disorders and diabetes. See claims 1, 3, 15, 18, paragraphs [0013], [0017], [0029]-[0031], [0034], [0035] and column 7, lines 36-55.

D3 describes the use of pyruvate and alpha-ketoglutarate to prevent glycation of proteins, which has been ascribed to be important in the pathogenesis of several secondary complications of diabetes, such as cataract and retinopathy (see abstract).

Claims 13-14 relate to the use of AKG or derivatives thereof for the prevention or treatment of a high plasma glucose condition, such as diabetes type I or II.

The subject-matter of claims 13-14 is novel and is considered to have an inventive step. None of the documents cited reveals that administration of AKG results in decreased absorption of glucose and therefore is suitable for treating diabetes.

Claims 15-20 relate to the use of AKG or derivatives thereof for improving absorption of amino acids and/or peptides.

The subject-matter of claims 15-20 is novel.

D1 is considered to represent the most relevant prior art.

The subject-matter of claim 15 differs from what is disclosed in D1 in that AKG is administered alone instead of in combination with calcium carbonate. Further, it differs in that the aim is to improve absorption (i.e. to alleviate malabsorption) of amino acids and/or peptides.

.../...

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**
Continuation of: Box V

In a response to the International Preliminary Examining Authority, the Applicant has explained that the use according to present claim 15 is intended for the treatment of patients who are eating proteins, but who cannot assimilate (absorb, utilise) amino acids/protein from food. In contrast, the aim in D1 is to improve amino acid metabolism and malnutrition in hemodialysis patients with chronic renal failure. Such patients are able to absorb amino acids. Instead, the problem is that they cannot metabolise (anabolise) amino acids and proteins, and therefore they are on a low protein diet which may result in malnutrition.

Thus, the problem solved by the invention according to claims 15-20 is different from the problem described in D1.

Therefore, the subject-matter of claims 15-20 is considered to show an inventive step.

The subject-matter of claims 13-20 fulfils the requirement of industrial applicability.

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## CLAIMS

1. A method for improving absorption of amino acids in a vertebrate, including mammal and bird, the method comprising administering to a vertebrate, including mammal and bird, in a sufficient amount and/or at a sufficient rate to enable a desired effect on amino acid absorption AKG, AKG derivates or metabolites, AKG analogues, or mixtures thereof.

2. The method according to claim 1, wherein the AKG, AKG derivates or metabolites, AKG analogues or mixtures thereof, are selected from the group consisting of alpha-ketoglutaric acid (AKG), ornitine-AKG, arginine-AKG, glutamine-AKG, glutamate-AKG, leucine-AKG, chitosan-AKG, and other salts of AKG with amino acids and amino acid derivates; mono- and di-metal salts of AKG such as CaAKG, $Ca(AKG)_2$, and NaAKG.

3. The method according to any of the claims 1-2, wherein the vertebrate is a rodent, such as a mouse, rat, guinea pig, or a rabbit; a bird, such as a turkey, hen, chicken or other broilers; farm animals, such as a cow, a horse, a pig, piglet or free going farm animals; or a pet, such as a dog, or a cat.

4. The method according to any of the claims 1-2, wherein the vertebrate is a human being.

5. The method according to any of the claims 1-4, wherein the amino acid is any essential amino acid.

6. The method according to claim 5, wherein the essential amino acid is isoleucine, leucine, lysine, and proline.

7. A method for decreasing absorption of plasma glucose in a vertebrate, including mammal and bird, the method comprising administering to a vertebrate, including mammal and bird, in a sufficient amount and/or at a sufficient rate to enable a desired effect on glucose absorption, AKG, AKG derivates or metabolites, AKG analogues, or mixtures thereof.

8. A method for preventing, inhibiting, or alleviating a high plasma glucose condition in a vertebrate, including mammal and bird, the method comprising administering to a vertebrate, including mammal and bird, in a sufficient

amount and/or at a sufficient rate to enable a desired effect on said condition, AKG, AKG derivates or metabolites, AKG analogues, or mixtures thereof.

9. The methods according to any of the claims 7-8, wherein the AKG, AKG derivates or metabolites, AKG analogues or mixtures thereof are selected from the group consisting of alpha-ketoglutaric acid (AKG), ornitine-AKG, arginine-AKG, glutamine-AKG, glutamate-AKG, leucine-AKG, chitosan-AKG and other salts of AKG with amino acids and amino acids derivates; mono- and di-metal salts of AKG such as CaAKG, and NaAKG.

10. The methods according to any of the claims 7-9, wherein the vertebrate is a rodent, such as a mouse, rat, guinea pig, or a rabbit; a bird, such as a turkey, hen, chicken or other broilers; farm animals, such as a cow, a horse, a pig, piglet or free going farm animals; or a pet, such as a dog, or a cat.

11. The methods according to any of the claims 7-10, wherein the vertebrate is a human being.

12. The methods according to any of the claims 8-11, wherein the high plasma glucose condition is Type I or Type II diabetes mellitus.

13. Use of AKG, AKG derivates or metabolites, AKG analogues or mixtures thereof, selected from the group consisting of alpha-ketoglutaric acid (AKG), ornitine-AKG, arginine-AKG, glutamine-AKG, glutamate-AKG, leucine-AKG, chitosan-AKG and other salts of AKG with amino acids and amino acids derivates; mono- and di-metal salts of AKG such as CaAKG, $CaAKG_2$, and NaAKG for the manufacture of a composition for the prevention, alleviation or treatment of a high plasma glucose condition.

14. The use according to claim 13, wherein the high plasma glucose condition is diabetes mellitus type I or II.

15. Use of AKG, AKG derivates or metabolites, AKG analogues or mixtures thereof, selected from the group consisting of alpha-ketoglutaric acid (AKG), ornitine-AKG, arginine-AKG, glutamine-AKG, glutamate-AKG, leucine-AKG, chitosan-AKG and other salts of AKG with amino acids and amino acids derivates; mono- and di-metal salts of AKG such as CaAKG, $CaAKG_2$, and NaAKG for the manufacture of a composition for improving absorption, altered

absorption, impaired absorption, and malabsorption of amino acids and/or peptides.

16. The uses according to any of the claims 13-15, wherein the composition is a pharmaceutical composition with optionally a pharmaceutically acceptable carrier and/or additives.

17. The uses according to any of the claims 13-15, wherein the composition is a food or a feed supplement.

18. The uses according to claim 17, wherein the food or feed supplement is a dietary supplement and/or a component in the form of solid food and/or beverage.

19. The uses according to any of the claims 13-18, wherein the AKG, AKG derivates or metabolites, AKG analogues or mixtures thereof, in the manufactured composition, is in a therapeutically effective amount.

20. The uses according to claim 19, wherein the therapeutically effective amount is 0.01-0.2 g/kg bodyweight per daily dose.